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Right fronto-parietal dysfunction underlying spatial attention in bipolar disorder

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Abstract

Although the neural underpinning of bipolar disorder (BD) is still unknown, recent research suggests that the right fronto-parietal cortex is particularly affected in BD patients. If this were true, we would expect atypical functional cerebral asymmetries in allocation of visuospatial attention. To test this hypothesis, euthymic BD patients and age- and gender-matched healthy controls were compared on the visual line-bisection task, a reliable measure of visuospatial attention, associated with right parietal function. Line bisection performance (i.e. absolute and directional bias) was compared between groups as a function of response hand and line position. The results showed a typical hand-use effect in healthy controls involving a larger leftward bias (i.e. pseudoneglect) with the left hand than with the right hand. Although euthymic BD patients did not differ from healthy controls in the overall accuracy (i.e. absolute bias), they differed significantly in the directional line bisection bias. In contrast to healthy controls, BD patients did not significantly deviate from the veridical center, regardless which hand was used to bisect horizontal lines. This finding indicates an atypical functional cerebral asymmetry in visuospatial attention in BD euthymia, supporting the idea of a dysfunction especially in the right fronto-parietal cortex.

Keywords: functional cerebral asymmetries; bipolar disorder; visuospatial attention;

1. Introduction

Bipolar disorder (BD) is a common mental illness with an overall lifetime prevalence of about 1% in the general population (Müller-Oerlinghausen et al., 2002). Typically, BD is characterized by a cyclic pattern of mood states that includes phases of depressed and elevated mood, as well as euthymic periods. The clinical presentation of BD ranges from hypomania and moderate depression to severe mania or depression with psychotic features, as well as mixed states (Müller-Oerlinghausen et al., 2002).

The neural underpinning of BD remains unclear. However, a right hemisphere involvement in BD has been suggested by findings of decreased gray matter volume in right prefrontal and parietal lobes (Lyoo et al., 2004; Adler et al., 2005) as well as cortical thinning in right superior parietal areas (Lyoo et al., 2006). In addition, neuroimaging and neurophysiological studies revealed atypical functional brain organization, particularly involving the right hemisphere rather than the left (e.g., Grisaru et al., 1998; Rubinsztein et al., 2001; Townsend et al., 2010). For example, a positron emission tomography study using a decision-making task, where participants were asked to choose between a red and a blue box to find a token, showed a decreased right superior frontal activation in manic BD patients compared to healthy controls (Rubinsztein et al., 2001). Also, functional magnetic resonance activation during an n-back task where subjects had to identify letters two positions back in a letter sequence, replicated prior findings of bilateral dorsolateral prefrontal cortex and parietal regions in healthy controls, whereas BD patients revealed reduced right parietal activation (Townsend et al., 2010). Moreover, a study (Grisaru et al., 1998) investigated the clinical properties of repetitive transcranial magnetic stimulation applied over the left and right prefrontal cortex. The results showed that manic symptoms of BD patients significantly improved after repetitive transcranial magnetic stimulation over the right prefrontal cortex compared to BD patients receiving repetitive transcranial magnetic stimulation of the left

prefrontal cortex. These findings could also have implications for atypical functional cerebral asymmetries (i.e. right hemisphere dysfunction) underlying acute mood in BD.

Atypical functional cerebral asymmetries particularly affecting frontal and parietal areas of the right hemisphere in BD have also been shown by a dichotic listening click detection task assessing selective attention (Yozawitz et al., 1979; Bruder et al., 1981). Bruder et al.'s (1981) dichotic listening paradigm involves the presentation of clicks to the right and left ear with an inter-aural delay. Healthy controls in this dichotic listening click detection task showed lower thresholds when the click in the left ear was presented before the click in the right ear (left ear advantage), suggesting a right hemisphere advantage. BD patients, however, revealed a significant right ear advantage in this task (Yozawitz et al., 1979; Bruder et al., 1981), suggesting atypical left hemisphere superiority in selective attention. The authors therefore conclude that this atypical functional brain organization in BD patients may have resulted from right hemisphere dysfunction.

In BD, right hemisphere dysfunction involving visuospatial functioning, has also been shown by visual half-field studies using the dot enumeration task (Bruder et al., 1989). Specifically, BD patients, in contrast to healthy controls, failed to show the expected left visual field (right hemisphere) advantage for reporting the number of dots presented within visual half-fields (Bruder et al., 1989, 1992, 1994). Moreover, an event-related potential study replicated the reduced left visual field (right hemisphere) advantage with the dot enumeration task. This study also revealed smaller N100 amplitude in BD patients for clicks localized in the left than right hemifield, again suggesting a right hemisphere dysfunction (Bruder et al., 1992). This effect was specific for depressive BD patients. In contrast, major depressive disorder patients and healthy controls did not show any functional cerebral asymmetries in N100. Although Bruder et al. did not localize the source of this effect, it is interesting to know that lesions in right parietal regions were associated with impaired dot

enumeration performance (Warrington and James, 1967), again suggesting right parietal dysfunction in BD patients.

Spatial attention is another key function of the right hemisphere. Although each hemisphere is involved in allocating attention towards the contralateral hemispace, it has been proposed that the right hemisphere allocates attention to both, the left and right hemispaces, suggesting its dominant role in spatial attention (Heilman and Valenstein, 1979; Heilman and Van Den Abell, 1980; Mesulam, 1981). A right parietal dysfunction in BD has been shown by a positron emission tomography study using a serial reaction time task, attributed to visuospatial function, in which participants are visually cued to press one of four buttons at a time (Berns et al., 2002). It has been shown that responses to this task involve manifestations of shifts of visuospatial attention to likely stimulus locations (Marcus et al., 2006). In Berns et al.'s study, BD patients exhibited significantly reduced activation in the right superior parietal cortex compared with healthy controls when finger sequence changed, which might have compromised visuospatial processing. However, Berns et al. employed a bimanual RT task, rather than examining one hand at a time, and therefore it is difficult to interpret the normal hemispheric pattern during bimanual performance.

A more reliable measurement of the right hemisphere dominance in spatial attention is the visual line-bisection task (e.g., Roig and Cicero, 1994; Brodie and Pettigrew, 1996; MacLeod and Turnbull, 1999; McCourt et al., 2001; Hausmann et al., 2002; Hausmann et al., 2003a; Hausmann et al., 2003b; Hausmann, 2005; for review see Jewell and McCourt, 2000). Participants are asked to bisect horizontal lines into two parts of equal length by marking the subjective midpoint of each line with a fine pencil. Patients with right inferior parietal lesions show a strong rightward bisection bias (e.g., Schenkenberg et al., 1980), which is explained as the result of the left hemisphere being exclusively concerned with attention to the contralateral right hemispace. Normal controls also show a bias but tend to systematically

bisect lines to the left of the objective middle, suggesting that although the right hemisphere is dominant in spatial attention and can direct attention to both sides of space, it slightly favors left hemispace (e.g., Bowers and Heilman, 1980). The stronger right hemisphere involvement in spatial attention during line bisection has been supported by neuroimaging and neurophysiological studies (Fink et al., 2000; Foxe et al., 2003; Waberski et al., 2008; Cicek et al., 2009). The right hemisphere dominance in allocating attention is also confirmed by the fact that the leftward bias is especially pronounced when subjects use their left hand (corresponding to the right hemisphere) to bisect lines (e.g., Roig and Cicero, 1994; Brodie and Pettigrew, 1996; MacLeod and Turnbull, 1999; McCourt et al., 2001; Hausmann et al., 2002; Hausmann et al., 2003a; Hausmann et al., 2003b; Hausmann, 2005; for review see Jewell and McCourt, 2000). Given that the left bias still exists when the right hand is used, this suggests interhemispheric spreading activation, probably via the corpus callosum, from the left hemisphere motor areas to the dominant attention network in the right hemisphere (McCourt et al., 2001). The role of the corpus callosum in visual line bisection is supported by studies on patients with callosal infarction (Kashiwagi et al., 1990; Corballis, 1995), patients with partial or complete commissurotomy (Heilman et al., 1984; Hausmann et al., 2003a) and younger children associated with immaturity of the corpus callosum especially in the posterior subareas (i.e., splenium).

Up to now, only one recent study has investigated visuospatial attention in BD (psychotic and non-psychotic) and healthy controls by applying a visual line-bisection task (Rao et al., 2010). This study revealed a leftward bias in both psychotic and non-psychotic BD patients compared to healthy controls when using the right hand. No such difference between BD patients and healthy controls was found for the left hand. This finding is surprising since a right hemisphere dysfunction in BD patients would predict a rightward bias which is similar to that of neglect patients with right hemisphere lesions. BD patients should

at least show a reduced leftward bisection bias (i.e. reduced pseudoneglect) that is usually found in normal controls, especially when the left hand is used to bisect lines (Milner et al., 1992). Rao et al.'s findings, however, did not follow this prediction. For the percentage deviation score, which takes line length into account, this study found an unusually large leftward bias (68.38 %) for the left hand in healthy controls, which is different from the leftward bias (i.e. pseudoneglect) of about 1-3% typically found in healthy controls. Due to this limitation further examination of visual line bisection in BD patients seems necessary.

BD seem to involve a hyperactivated right fronto-parietal network particularly implicated in emotion perception (e.g., Blumberg et al., 2005; Wessa et al., 2007; Robinson et al., 2008; Pavuluri et al., 2009; Chen et al., 2010; Lee et al., 2010; Morris et al., 2012; Liu et al., 2012), but also supported by the right (fronto) parietal dysfunction shown by the visual field, dichotic listening and positron emission tomography studies mentioned above (Bruder et al., 1981, 1989, 1992, 1994; Berns et al., 2002). Based on these findings, we hypothesis that a right hemisphere dysfunction should particularly affect the left hand bisection bias in BD patients compared to healthy controls.

2. Method

2.1 Participants

Twenty-two patients (13 women) with BD (Age: 44.59 ± 9.97 years) were recruited from Northumberland NHS Foundation Trust and Tees, Esk and Wear Valleys NHS Foundation Trust. The diagnosis of BD was confirmed by an independent psychiatrist. All individuals fulfilled the following inclusion criteria: (1) a diagnosis of BD, type I, according with the Structured Clinical Interview for DSM-IV (First et al., 1995), (2) no current concomitant Axis I disorder, and (3) no history of medical or neurologic condition. Individuals were also excluded if they met the DSM-IV diagnosis for anxiety disorders or substance abuse within the preceding six months. BD patients were clinically stable outpatients at the time of the

study. The current depressive symptoms were assessed using the 17-item Hamilton Rating Scale for Depression (Hamilton, 1960). The manic symptoms were assessed with the Young Mania Rating Scale (Young et al., 1978).

As a group [Hamilton Rating Scale for Depression = 3.05 ± 1.98 (0–7) and Young Mania Rating Scale = 5.18 ± 4.23 (0–10)] and based upon symptom ratings (Hamilton Rating Scale for Depression ≤ 7 , Young Mania Rating Scale ≤ 10), BD patients were euthymic on the day of the study. Previously anxiety symptoms were present in three patients. Five patients had a history of alcohol or substance abuse. Fifteen of the BD patients were taking mood-stabilizing medications; eight patients were taking antidepressants. In addition, twelve patients were receiving atypical antipsychotic. None of the patients with BD were experiencing psychotic symptoms at the time of the assessment.

Eighteen healthy controls (Age: 41.94 ± 10.37 years; 10 women) were recruited through local announcements (e.g. local post office, community library, Durham University, etc.). Control participants were matched for age, sex, and education and had no history of any Axis I disorder and no history of affective disorder or schizophrenia in first-degree relatives.

BD patients and healthy controls were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). The asymmetry-index provided by this test is calculated as $((R-L)/(R+L)) \times 100$ resulting in values between -100 and +100. This range describes the continuum from extreme sinistrality to extreme dextrality. The handedness scores for the BD patients (88.99 ± 12.51) and healthy controls (87.00 ± 16.83) did not significantly differ ($t(38) = -0.43$, n.s.).

After receiving a complete description of the study, written informed consent was obtained from each participant. The study was approved by the regional ethics committee from the NHS and Durham University Ethics Advisory Committee. All participants received £20 for participating in the study.

2.2 Procedure and Materials

The line-bisection task was identical to that used in a previous study (e.g., Hausmann et al., 2002, 2003a,b; Hausmann, 2005). Seventeen horizontal black lines 1 mm wide were printed on a white sheet of paper (21 cm x 30 cm). The lines ranged from 100 to 260 mm in length in steps of 20 mm. The mean length was 183.5 mm. They were pseudorandomly positioned so that seven lines appeared in the middle of the sheet, five lines appeared near the left margin, and five lines appeared near the right margin. The lateralized lines were 13 mm away from the margin. The line lengths for the seven centered lines were 12 cm (one line), 18 cm (two lines), 22 cm (two lines), 24 cm (two lines; $M = 20$ cm) and 10 cm, 14 cm, 16 cm, 20 cm, and 26 cm ($M = 17.2$ cm) for the five left- and five right-lateralized lines, respectively. The sheet was laid in front of the participant's midline. Participants were instructed to bisect all lines into two parts of equal length by marking the subjective midpoint of each line with a fine pencil. All participants completed the task with one hand and then repeated it with the other in a balanced order. The experimenter covered each line after it was marked to ensure that the participants were not biased by their previous choices. There were no time restrictions. The deviations to the left or to the right of each marked line were carefully measured to 0.5 mm accuracy. The percentage deviation score for each line was computed as follows: $[(\text{measured left half} - \text{true half}) / \text{true half}] \times 100$. This measure is comparable with that used in other studies (Scarisbrick et al., 1987; Shuren et al., 1994) and takes individual line length into account. We then computed the mean score for all lines separately for each hand. Negative values indicate a left bias, and positive values indicate a right bias. The degree of left bias was statistically compared with a deviation score of zero (true center of the line) by calculating one-sample t-tests (Bonferroni adjusted) for each group and each hand. The

absolute deviation bias (in millimeters) was also calculated, indicating the overall accuracy independent of its direction.

3. Results

3.1 Absolute line bisection bias (accuracy)

To investigate whether euthymic BD patients and healthy controls differed in accuracy, absolute deviations in visual line bisection were compared between both groups. Absolute biases were entered into a 2 x 2 split-plot analysis of variance (ANOVA), with hand-use (left hand, right hand) as within-subject factor, and group (patients, controls) as between-subjects factors. The ANOVA revealed that neither the main effect of group, $F(1, 38) = 1.54$, $p > 0.10$, $\eta_p^2 = 0.04$, nor any other effect approached significance (all $F < 0.89$, n.s.), indicating that BD patients bisected lines as accurately as healthy controls across all conditions. Absolute deviation bias of left and right hand bisections for healthy controls and BD patients are shown in Table 1.

Hand	HC	BD
Left hand	4.19 ± 1.44	4.5 ± 1.68
Right hand	3.90 ± 1.21	4.68 ± 1.75

Table 1. Absolute deviation bias (Mean ± SEM) of left and right hand bisections for healthy controls (HC) and bipolar disorder patients (BD).

3.2 Directional line bisection bias (laterality)

Percentage deviation scores of both groups were subjected to a 2 x 2 split-plot ANOVA, with hand-use (left hand, right hand) as within-subject factor, and group (patients, controls) as between-subjects factors. A significant intercept effect refers to the grand mean of all the data

and suggests that the overall mean is not equal to zero (perfect symmetry). As indicated by the significant intercept effect of the present study, there was an overall leftward bias, $F(1, 38) = 5.58$, $p < 0.05$, $\eta_p^2 = 0.13$, suggesting a right hemispheric superiority in allocating attention. However, the main effect of group was not significant, $F(1, 38) = 0.84$, $p > 0.10$, $\eta_p^2 = 0.02$. The analysis also revealed a significant main effect of hand use, $F(1, 38) = 4.27$, $p < 0.05$, $\eta_p^2 = 0.10$, with a larger leftward bias when using the left hand compared with the right hand. The interaction between hand use and group was also significant, $F(1, 38) = 6.44$, $p < 0.05$, $\eta_p^2 = 0.15$. Post hoc paired t -tests revealed a significant hand use difference in healthy controls only ($t(17) = 3.17$, $p < 0.025$). There was no effect for hand use in BD patients ($t(21) = 0.34$, n.s.). As shown in Figure 1, the control group revealed the well-known and significant left bias when using the left hand ($t(17) = 4.69$, $p < 0.025$) and no bias for the right hand ($t(17) = 0.12$, n.s.). In contrast, BD patients did not exhibit a significant bias with either hand (both $t > 0.87$, n.s.). Likewise, the comparison of the left bias between groups was significant for the left ($t(38) = 2.46$, $p < 0.025$) but not for the right hand ($t(38) = 0.74$, n.s.).

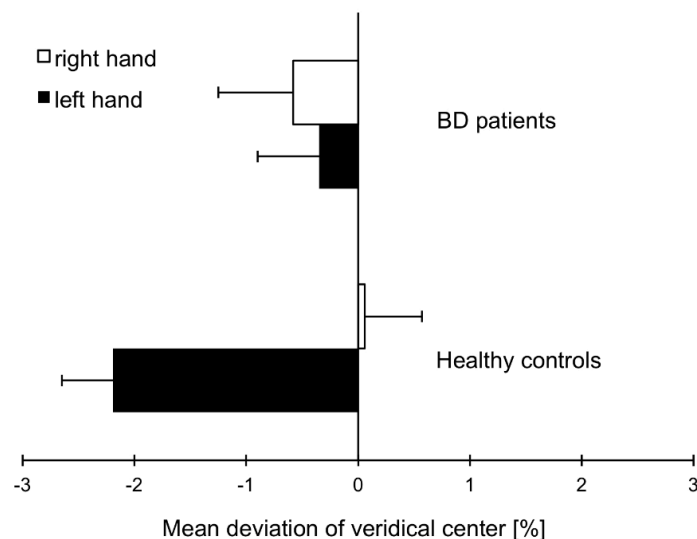


Figure 1. Mean deviations (%) and standard error means from the true center during line bisection for bipolar patients (top) and healthy control (bottom) for the left hand (black bars) and right hand (white bars). Data are collapsed across line position.

To investigate potential medication effects on line bisection, percentage deviation scores of only BD patients were subjected to a 2 x 2 split-plot ANOVA, with hand-use (left hand, right hand) as within-subject factor, and ‘antidepressants’ (medication users: $n = 8$, non-users: $n = 14$) as between-subjects factors. The ANOVA revealed that the main effect of ‘antidepressants’ approached significance, $F(1, 20) = 3.76$, $p < 0.10$, $\eta_p^2 = 0.16$, indicating a non-significant trend for a difference between the typical overall left bias in medication users (-1.72 ± 1.72 , $t(7) = 3.92$, $p < 0.01$) and the reduced bias in non-users (0.25 ± 0.61 , $t(13) = 0.34$, n.s.). No other effect approached significance (all $F < 2.12$, n.s.). The same ANOVA did not reveal any effects when ‘antipsychotics’ (medication users: $n = 12$, non-users: $n = 10$) was used as between-subject factor (all $F < 1.07$, n.s.).

4. Discussion

The present study replicated the well-known overall left bias in visual line bisection (i.e. pseudoneglect), which has consistently been found in studies using the line bisection paradigm in neurologically normal individuals (McCourt and Olafson, 1997; McCourt and Jewell, 1999; Jewell and McCourt, 2000 for a review). Moreover, the present study found the typical hand-use effect in healthy controls (e.g., Roig and Cicero, 1994; Brodie and Pettigrew, 1996; MacLeod and Turnbull, 1999; McCourt et al., 2001; Hausmann et al., 2002; Hausmann et al., 2003a; Hausmann et al., 2003b; Hausmann, 2005; for review see Jewell and McCourt, 2000), that is, a significantly larger left bias with the left than the right hand. The results for healthy controls are also in line with functional magnetic resonance research showing that line bisection judgments to be associated with activation in the right superior posterior and right inferior parietal cortices (Fink et al., 2000). This activation seems to be promoted by using the left hand, which is assumed to be particularly under the control of the attention-dominant right hemisphere (Milner et al., 1992).

Although the overall left bias did not significantly differ between groups, BD patients did not show the typical leftward bias with the left hand. In fact, the bisection bias with either hand did not significantly differ from the veridical center. It seems that BD patients placed the line bisection mark closer to the veridical center. The analysis of the absolute bias (regardless of its direction) suggests, however, that BD patients and healthy controls were similarly accurate in line bisection. The strongly reduced directional left hand line bisection bias in BD patients indicates a reduced functional cerebral asymmetry in spatial attention, suggesting a dysfunction of parietal areas of the right hemisphere.

To the best of our knowledge, the only available line bisection study on BD is the study by Rao and colleagues (2010). Among a number of limitations mentioned previously, the study failed to show the well-known pseudoneglect in healthy controls. In fact, the percentage deviation score for the left hand in healthy controls showed an unusually large left bias (68.38 %). The deviation biases in healthy controls usually ranges from 1% to 3% with respect to the length of the line (for a review see Jewell and McCourt, 2000). The left hand line bisection bias of 2% found in normal controls within the present study falls into this expected range. It is unlikely that methodological issues can account for these unexpected findings. The line bisection task used in Rao et al. and the present study overlaps considerably in various aspects. For example, the line bisection task used in the present study included horizontal lines presented in the middle or close to the left and right margins of the sheet. Similarly, Rao et al. (2010) also used lines presented close to the left and right margins. Also, the present study used line lengths ranging from 100-260 mm (in steps of 20 mm). Rao et al.'s study used line lengths between 70-160 mm (in steps of 10 mm).

Supporting our prediction of a right hemisphere dysfunction particularly affecting left hand bisection in BD, the present findings show a hand use difference between BD patients and healthy controls mainly driven by the reduced leftward bias in BD patients when using

the left hand (corresponding to the right hemisphere). Although this finding is difficult to explain in terms of an overactivated right hemisphere in BD, it supports the assumption of right parietal dysfunction in BD patients (Bruder et al., 1981, 1989, 1992, 1994; Berns et al., 2002). The non-significant left hand bias, as found in BD patients within the present study, suggests an underactivation of the right parietal cortex (McCourt et al., 2001). In line with a number of recent studies (Lee et al., 2010; Kim et al., 2012; Liu et al., 2012) parietal regions are especially involved in the pathophysiology of BD. However, two of these magnetoencephalographic studies also showed right parietal hyperactivity in an implicit emotional faces task in BD (Lee et al., 2010; Liu et al., 2012). Specifically, Lee and colleagues (2010) examined BD and major depressive disorder patients using an implicit paradigm requiring participants to judge the gender (a non-emotional facial cue) of emotional faces while recording event related magnetoencephalographic signals. In contrast to major depressive disorder patients and healthy controls, BD patients exhibited an increased activity in the right inferior parietal gyrus (Lee et al., 2010). However, differences between the present study (using a line bisection task that is unrelated to emotional processing and measures spatial attention), and both magnetoencephalographic studies, (using arousing emotional (face) stimuli), may explain discrepancies in the direction of right fronto-parietal activation.

The present study confirms previous studies that have used the visual line bisection task as a valuable tool for assessing the functional brain organization associated with the pathophysiology of different neuropsychiatric disorders (Barnett, 2006; McCourt et al., 2008). For example, line bisection studies in children with attention-deficit hyperactivity disorder have consistently shown a rightward bias in spatial attention, suggesting a right hemisphere inefficiency associated with symptoms of severe impulsivity and/or hyperactivity (Sheppard et al., 1999; Manly et al., 2005; Rolfe et al., 2008; Waldie and Hausmann, 2010).

Also, the leftward bias in line bisection (i.e., pseudoneglect) that usually characterizes the right-hemisphere dominance for the allocation of visuospatial attention observed in neurologically normal subjects was increased in dependent personality disorder (Wang et al., 2003), and similar to the present study, significantly reduced in schizophrenia (Mather et al., 1990; Barnett, 2006; Zivotofsky et al., 2007; McCourt et al., 2008). Thus, these findings suggest that the visual line bisection is sensitive to atypical functional brain organization across different neuropsychiatric disorders.

Adding to the line bisection literature in neuropsychiatric disorders, the present study found a reduced leftward bisection bias in euthymic BD patients suggesting a reduced dominance of the right hemisphere in spatial attention, perhaps as a result of functional alterations within the right parietal cortex. In contrast to manic or depressive BD episodes, euthymic BD patients experience a state that is close to ‘normal’ mood. Therefore, the present findings in BD euthymia suggest an atypical brain organization in spatial attention, perhaps as a result of functional alterations within the right parietal cortex.

The group of BD patients in the present study was quite heterogeneous with respect to their medication. Although we found some evidence for a difference in the directional line bisection bias between users and non-users of antidepressants (i.e. medication-users showed a typical leftward bias, whereas non-users deviated slightly to the right of the center), this effect should be interpreted with caution, because of the small sample size of BD patients using antidepressants. However, the results show that medication effects cannot be ruled out. Whether antidepressants affect line bisection directly by modulating the lateralized serotonergic system of cortical/subcortical areas (Kranz et al., 2012) that are involved in spatial attention, and/or indirectly by changing the patients’ emotional state, which is known to affect functional cerebral asymmetries even in healthy subjects (e.g. Dyck et al., 2011;

Najt et al., 2013; Papousek et al., 2009; Schock et al., 2012), needs further consideration in future studies.

It should be noted that a similar right hemispheric dysfunction was found in BD patients during both manic and depressive episodes (Bruder et al., 1981, 1989, 1994; Yozawitz et al., 1979). If this atypical functional asymmetry is independent of patients' clinical state, the right hemispheric dysfunction may be considered as a 'trait marker' of BD. However, to directly test this idea, future studies should also include tasks for which the left hemisphere is dominant. In addition, to better differentiate between trait and state aspects, future studies should test BD patients during both euthymic and mood episodes, and their symptom-free first-degree relatives, who are known to show similar cognitive impairments, albeit to a lesser degree (Arts et al., 2008).

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